REMARKS

Upon entry of the amendments herein, claims 2-9, 11-17, 19-23, 25, 26, 28-33, 41, 42, 47, 54 and 61 are pending in the application. Claims 9, 16, 19, 25, 28 and 32 have been amended; and claims 10, 18, 27, 43-46, 48-53, 55-60, 62 and 63 have been cancelled. No new matter has been introduced by any of these amendments.

Applicants note the Examiner's acknowledgement that, although only claims 2, 4-8, 41 and 42 were examined in the outstanding Office Action, claims 2-23, 25-33 and 41-63 remain pending in the application.

In their last response, Applicants reminded the Examiner of his indication that, upon determination of allowable scope of elected subject matter, "kit" claims and method-of-use claims of appropriate scope would also be rejoined for further examination. In response, the Examiner suggested that the limitations in claim 2 with respect to the CPU inhibitor be introduced into the kit claims. By amendment herein, Applicants have implemented the Examiner's suggestion. The method-of-treatment claims have also been amended in a parallel way in anticipation of their being rejoined. Thus, claims 10, 18 and 27 have been cancelled and their limitations incorporated into claims 9, 16 and 25, respectively. In the wake of the

cancellation of claims 10, 18 and 27, a number of claims dependent therefrom have also been cancelled.

The Examiner also indicated that he would consider rejoining the CPU inhibitor compounds of Group 2 to the compounds of Group 1, upon determination of the patentability of the latter genus of compounds. It should be pointed out that, in anticipation of this eventual rejoining of Groups 1 and 2, claims 9, 16 and 25 have been amended so that they recite the compounds of both claims 2 and 3.

Claims 2, 4-8, 41 and 42 have been rejected under 35 USC §103 as being obvious over Ondetti et al., Biochem. **18**, 1427 (1979) in view of U.S patent No. 5,993,815 to Bajzar et al. further in view of U.S. Patent No. 5,955,433 to Bylund et al. or International Publication No. WO 94/293,336 of Antonsson et al or International Publication No. WO 96/16671 of Löfroth et al. This rejection hinges on the Examiner's assertion that the primary reference discloses a particular compound, SQ 24,798, as an inhibitor of CPU and that this compound falls within the scope of instant claim 2. However, Ondetti does not disclose this compound or any others to be inhibitors of CPU.

In fact, Ondetti and coworkers were concerned with inhibitors of Carboxypeptidase A ("CPA") and carboxypeptidase B ("CPB"); it is these enzymes that Ondetti discloses to be inhibited by SQ 24,798. CPU was not even known at the time and

would not be known for a number of years following. Much confusion has arisen out of the various names given to the different enzymes that are labeled as carboxypeptidases. For example, CPU is also known as "plasma carboxypeptidase B." However, it is well known that CPU and CPB are not the same enzyme nor do they have the same properties.

Applicants provide herewith for the Examiner's information copies of two references which bear on the matter. These are the article by Skidgel in "Zinc Metalloproteases in Health and Disease," N. Hooper, Ed., Taylor & Francis, London, pages 241-283 (1996) and that of Bouma et al. Thrombosis Res. **101**, 329-354 (2001). The Examiner's attention is particularly drawn to pages 243 and 244 of Skidgel and pages 329-331 of Bouma. From this disclosure, it can be seen, in the first place, how confusion easily arises as the identification of the various enzymes considered to be in the carboxypeptidase family. Furthermore, it can be seen that, unlike CPA and CPB, CPU is found in the liver and blood and has a role in coagulation and fibrinolysis. CPA and CPB, on the other hand, are found in the pancreas and are involved in the digestive system.

Thus, regardless of whether or not the primary reference discloses a compound within the scope of instant claim 2, said compound is not taught to be an inhibitor of CPU. In fact, there is no teaching in the primary reference of CPU in any

context, let alone inhibition of CPU. Thus, furthermore, regardless of whether or not the cited secondary references teach what the Examiner alleges they teach, the primary reference is fundamentally deficient, and the secondary references cannot be combined with the primary reference to provide a teaching or even suggestion to make the instantly claimed invention.

The Examiner has also leveled three rejections of the claims as being obvious over a second Ondetti primary reference in combination with various secondary references. These combinations are U.S. Patent No. 4,177,277 to Ondetti 1) in view of Bajzar or Boffa, 2) in view of Grainger or Watson or Franson and 3) in view of Bylund or Löfroth or Antonsson. Again, as with the other Ondetti primary reference, this one does not teach CPU or inhibitors of CPU. CPU was not even known at the time and the "carboxypeptidase B-like enzymes" referred to by Ondetti in a passage singled out by the Examiner are not the CPU of the present invention. The Examiner is again reminded of the differences in location, function and properties between CPU and CPB that are set forth in, for example, the Skidgel and Bouma articles provided herewith. Thus, for the same reasons that the first-cited Ondetti primary reference is fundamentally deficient, so too is the second-cited Ondetti primary reference, and the secondary references cannot make up

for the deficiency and cannot be said to lead one of skill in the art to the instant invention when combined with the primary reference.

The claims have also been rejected as being obvious over the primary reference of U.S. Patent No. 6,126,939 to Eisenbach-Schwartz et al. in view of Grainger or Watson or Franson. This rejection hinges on the assertion that the primary reference teaches the dipeptide Arg-Cys for the treatment of various inflammatory disorders, that this dipeptide falls within the scope of instant claim 2 and that inhibition of CPU is an inherent property of this compound.

It is not seen what the primary reference has to do with CPU or inhibition of CPU. According to Eisenbach-Schwartz (see, e.g., column 7, lines 47-56), the disclosed peptides have macrophage inhibitory and/or T cell inhibitory activity and, thus, anti-inflammatory activity. The peptides are also said to have anti-immune activity. In view of the known properties and location of CPU and the uses described for the instantly claimed formulations comprising CPU, the assertion that the teaching of the primary reference inherently discloses the instant invention is completely without merit. The mechanism and factors involved in the reduction of inflammation associated with immune responses are so far removed from the mechanism and factors involved in the diseases to be treated with the present

invention that an invocation of inherency cannot be supported. The Examiner asserts that the inhibition of CPU by the cited dipeptide is inherent, "absent evidence to the contrary." However, under the circumstances, it is the Examiner who must provide evidence for his assertion, given the complete disparity between what would be required to achieve inhibition of CPU and inhibition of, for example, T cell activity, and the expected utilities associated with such inhibitions.

Thus, whether or not the cited dipeptide falls within the scope of instant claim 2, the cited primary reference is fundamentally deficient in that it has nothing to do with inhibition of CPU or treatment of conditions that might respond to such inhibition. Furthermore, the cited secondary references cannot make up for this fundamental deficiency, and one of ordinary skill in the art would not be led by the combination of references to the presently claimed invention. This rejection cannot stand and should be withdrawn. Withdrawal is respectfully requested.

The Examiner has leveled a second obviousness rejection over the primary reference of Eisenbach-Schwartz, this one in view of Antonsson. For the same reasons set forth above, the primary Eisenbach-Schwartz reference is fundamentally deficient in having nothing to do with inhibition of CPU or treatment of conditions that might respond thereto; CPU is not mentioned in

the reference. There is nothing in the teaching of the primary reference to even remotely suggest that the dipeptide would serve as an inhibitor of CPU or would be useful in the treatment of the diseases recited in the invention as presently claimed. Applicants do not contest the assertion that the primary reference teaches a possible treatment of arthritis and that arthritis can be called an inflammatory disorder. However, this is irrelevant in the context of the present invention. Thus, similarly to the first Eisenbach-Schwartz rejection, the primary reference is fundamentally deficient and the cited secondary art cannot be said to make up for the deficiencies and lead one of ordinary skill in the art to the presently claimed invention.

The Examiner is also reminded of the unexpected, and previously unknown, effects observed when a combination of a CPU inhibitor and a thrombin inhibitor according to the instant invention is administered. In attempting to justify the prior art rejections, the Examiner refers in several instances to the alleged motivation to combine a CPU inhibitor with a thrombin inhibitor "for additive effects."

In the first place, Applicants reemphasize that, for all the reasons set forth above, there is no motivation provided by the various combinations of cited references to combine such agents for any reason. Secondly, even if the Examiner were

correct in alleging this motivation, Application have demonstrated effects well beyond mere additivity.

On, for example, page 3, lines 3-8 of the instant specification, it is disclosed that the "combination of a CPU inhibitor and a thrombin inhibitor potentiates anti-thrombin effects, thereby reducing the risk for thrombosis and hypercoagulability in blood and tissues in mammals." This is borne out by the data shown in Tables I-III in the specification. These data show that the combination of inhibitors has far greater potency than the sum of the effects of the inhibitors when they are administered individually. Furthermore, the sum of the effects of the two inhibitors when administered individually at given dosages can be matched or even increased upon administration of lower dosages of each of the inhibitors in combination. Such findings satisfy the criteria for nonobviousness in accordance with statute.

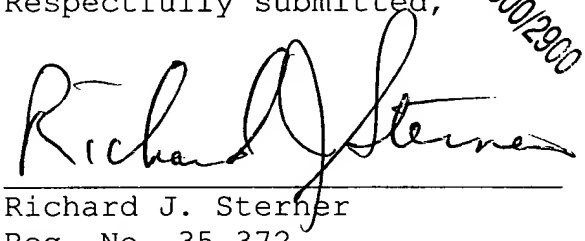
For all of the reasons set forth above, the Examiner has not established a prima facie case of obviousness; the claims currently being considered are allowable. With respect to the issue of rejoined subject matter, Applicants have taken the Examiner's suggestion and amended the kit and method-of-treatment claims so that their scope is commensurate with the presently pending formulation claims. Accordingly, the application is in condition for rejoining of said claims, as

well as the subject matter recited in claim 3. Allowance of the application with the claims previously considered by the Examiner and the rejoined claims is respectfully requested. Should any other matters require attention prior to allowance, it is requested that the Examiner contact the undersigned.

The Commissioner is hereby authorized to charge any fees which may be due in connection with this communication to Deposit Account No. 23-1703.

Dated: December 10, 2003

Respectfully submitted,



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Enclosures